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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **A BUFFERED POLYOL-HORMONE MIXTURE FOR USE IN CHRONIC PARENTERAL HORMONE ADMINISTRATION.**

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DIABETOLOGIA, vol. 19, 1980, pages 1-9; W.D. LOUGHEED et al.: " Insulin aggregation in artificial delivery systems"

ARTIFICIAL SYSTEMS FOR INSULIN DELIVERY, 1983, pages 83-94, Raven Press., New York, US; J. BRANGE et al.: "Properties of insulin in solution"

The file contains technical information submitted after the application was filed and not included in this specification

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Example 3

Effect of buffering with sodium bicarbonate or sodium phosphate on the extent of insulin oligomer formation. After incubation in glass vials at 37°C for four weeks, sodium bicarbonate (12 mM) decreased the amount of insulin-polymer formation in 80 per cent glycerol when compared to insulin in glycerol without bicarbonate. Further addition of 54 mM sodium phosphate decreased the formation of polymers still further.

The biological activity of this insulin/glycerol/bicarbonate/phosphate mixture was tested in a dog previously made diabetic with alloxan according to the standard technique described by applicant and colleagues (Surg. Gynecol. Obstet., 1982; 155: 860—864). The insulin delivered intravenously in this animal from an implantable pump was either the insulin/glycerol/bicarbonate mixture described above, or an identical solution containing in addition (final concentration) 54 mM sodium phosphate, pH 7.0. To determine whether the insulin actually delivered from the pump's infusion cannula retains biological activity during a three week flow cycle, the effects of alternating cycles of phosphate buffered and unbuffered insulin on fasting plasma glucose levels were compared at insulin delivery rates of 22 units/day. The phosphate-buffered solutions clearly prevented the gradual increase in fasting plasma glucose concentrations that occurred late in a three week flow cycle without phosphate. The addition of bicarbonate and phosphate buffers to the insulin/glycerol mixture appears to be largely effective in preventing the glycerol-induced formation of presumably inactive insulin oligomers.

Although the invention has been described with particular reference to the use of glycerol, other biocompatible C—4 to C—18 polyols, including sugars, behave similarly to glycerol as protectors of protein structure and function. Exemplary of such other polyols are C—4: erythritol; C—5: arabinose, xylose, ribose, adonital (ribitol) and arabitol; C—6: rhamose, inositol, fructose, galactose, glucose, mannose and sorbose, C—12: maltose and sucrose; and C—18: melezitose and raffinose. Where solid polyols are used they are dissolved in the standard aqueous insulin solution, or first prepared as an aqueous solution and admixed with the insulin, to provide a final concentration of polyol in the solution of 10 to 90% weight/volume, and preferably 40 to 80%. Similarly, although the invention is described with particular reference to solubilization of insulin, other infusible hormone are subject to the same precipitation problems, including growth hormone or glucagon.

The specific embodiments described are given by way of example and illustration of the invention.

Claims

1. A protein hormone solution suitable for parenteral administration at a low flow rate to a chronically ill patient suffering from a hormone-deficiency disease from a drug delivery device that depends on the fluidity of the infusate for proper functioning, said solution comprising a polyol having 3 to 18 carbon atoms in an amount between 10 and 90 per cent by volume, effective to prevent precipitation of the protein hormone, and a buffer system at a concentration between 1 mMolar and 1000 mMolar sufficient to maintain a pH within one unit of the optimum pH of said protein hormone whereby the biological activity of the hormone-polyol solution is maintained during extended periods of storage within the drug device.

2. A solution according to claim 1 comprising from 40 to 80 per cent by volume of said polyol.

3. A solution according to claim 1 or claim 2 wherein the polyol is selected from glycerol, erythritol, arabinose, xylose, ribose, adonital (ribitol), arabitol, rhamose, inositol, fructose, galactose, glucose, mannose, sorbose, maltose, sucrose, melezitose and raffinose.

4. A solution according to any one of claims 1 or 3 wherein said polyol is glycerol.

5. A solution according to any of claims 1 to 4 wherein said buffer system is a phosphate buffer.

6. A solution according to any of claims 1 to 5 wherein said protein hormone is insulin.

7. An insulin solution suitable for parenteral administration at a low flow rate to a chronically ill patient suffering from diabetes from a drug delivery device that depends on the fluidity of the infusate for proper functioning said solution comprising a polyol in an effective amount between 40 and 80 per cent by volume, effective to prevent precipitation of the insulin, and a sodium phosphate buffer system in concentration between 1 mMolar and 1000 mMolar sufficient to maintain a pH within one unit of the optimum pH of said insulin whereby the biological activity of the insulin-polyol solution is maintained during extended periods of storage within the drug device.

8. A solution according to claim 7 wherein said polyol is glycerol and said buffer system is sodium phosphate in combination with sodium bicarbonate.

9. A solution according to any of the preceding claims contained in the storage chamber of an implanted drug delivery device.

Patentansprüche

1. Proteinhormonlösung zur parenteralen Verabreichung bei niedriger Flußrate über eine Medikamentenabgabevorrichtung, deren richtige Funktion von der Fluidität des Infusates abhängig ist, an einen chronisch kranken Patienten, der an einer Hormonmangelkrankheit leidet, wobei die Lösung ein Polyol mit 3—18 Kohlenstoffatomen in einer Menge von 10—90 Vol.% umfaßt, die ein Ausfällen des Proteinhormons verhindert, und ein Puffersystem in einer Konzentration von 1 mMolar bis 1000 mMolar